

Abstract

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Project Title: High Throughput Screening of Select Orphan Nuclear Receptors

Abstract: DESCRIPTION (provided by applicant): Nuclear receptors are excellent targets for drug design. Orphagen has developed a 384-well assay for three orphan nuclear receptors that have not yet been characterized at a pharmacological level. Basic biological studies suggest that these targets have therapeutic potential in treatment of obesity, prostate cancer, metabolic disease (including type 2 diabetes), and sleep disorders. X-ray crystallography shows that the three receptors have small molecule binding pockets typical of the nuclear receptor family. To explore their potential as novel drug targets, however, small molecule ligands must be synthesized that are bioavailable and pharmacologically active in animal models of disease. A critical first step is the identification and confirmation of hits in high throughput screening (HTS) of diverse small molecule libraries. We propose screening of the three receptors in parallel in a cell-based assay for receptor-mediated gene transcriptional activity. Because the shapes of the small molecule binding pockets for each of the three receptors are substantially different, spurious hits (1-2% of most libraries) are easily identified since they affect all three receptors in the same way, whereas candidate hits will regulate one of the three receptors selectively. These candidate hits are confirmed in dose responsive transcriptional assays. In follow-on studies supported by current SBIR grant funding to Orphagen from the NIH, a secondary cell-free assay that measures compound binding to each of the purified receptors will be developed to substantiate ligand interaction. The characterized receptor assays, along with proven agonist or antagonist ligands, will provide a solid foundation for new drug discovery.

Relevance to Public Health: Unexplored drug targets, such as the orphan nuclear receptors, are sources of potential new drug classes for entirely new approaches to chronic disease. Interest in these targets by the pharmaceutical industry is low since they are at the very beginning of the drug discovery pipeline. Therapeutic areas that may be addressed by the studies described here are: type 2 diabetes, obesity, insomnia and other sleep disorders, and prostate cancer. The proposed studies, if successful, will provide workable and proven drug discovery technology for these targets where none exists today.

Thesaurus Terms:

High throughput screening, Orphan Nuclear Receptors, cell-based assay, obesity, prostate cancer, metabolic disease, type 2 diabetes, insomnia, sleep disorders, cell-free assay, compound binding, potential new drug classes

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